Remarks

Claims 1-11 are now pending in this application. Claims 12-60 are canceled without prejudice to Applicants' rights to pursue the subject matter thereof in one or more divisional, continuation, or continuation-in-part applications. Claim 5 is amended to correct a typographical error. No new matter has been introduced.

The Rejection Under 35 U.S.C. § 112, ¶ 1, Should Be Withdrawn

On pages 3-5 of the Office Action, claims 1-11 are rejected under 35 U.S.C. § 112, ¶ 1, as allegedly failing to comply with the written description requirement. In sum, it is alleged that "the support in the specification is not adequate for the claim to the treatment of any primary or metastatic cancer comprising administering ... any topoisomerase inhibitor ..." Office Action, pages 3-4. Applicants respectfully traverse this rejection.

As the Examiner is well aware, the essential question in a written description requirement is whether "the description clearly allow[s] persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 108, 1012 (Fed. Cir. 1989). While a question as to whether a specification provides an adequate written description may arise in the context of an original claim which is not described sufficiently, there is a strong presumption that an adequate written description is present in the specification as filed. *Manual of Patent Examining Procedure* ("MPEP") § 2163.03 (emphasis added). Accordingly, the examiner has the initial burden of presenting by a preponderance of the evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. MPEP § 2163.04 (citing *In re Wertheim*, 521 F.2d 257, 263 (C.C.P.A. 1976)). A general allegation of "unpredictability in the art" is not a sufficient reason to support a rejection for lack of adequate written description. MPEP § 2163.04.

As the Examiner correctly recognized, the treatment of colorectal cancer by administering thalidomide and irinotecan is successfully demonstrated in this application at pages 31-32 of the specification. Detailed procedures of treating various cancers by administering thalidomide with other topoisomerase inhibitors are also described, for example, at pages 32-35 of the specification. Furthermore, it was well-known in the art at the time of this invention that various topoisomerase inhibitors are effective in treating various types of cancers, albeit with certain adverse

effects that could limit the amount or dose of the topoisomerase inhibitor that can be administered to patients. Therefore, Applicants respectfully submit that the claims 1-11 are adequately supported by the specification and the knowledge that was possessed by one of ordinary skill in the art. Applicants further submit that the Examiner has not met his initial burden of establishing *prima facie* case of lack of written description, as an allegation of "unpredictability in the art" is not sufficient to support such a rejection. MPEP § 2163.04.

For the foregoing reasons, Applicants respectfully request that the rejection under 35 U.S.C. § 112, ¶ 1, be withdrawn.

The Rejection Under 35 U.S.C. § 112, ¶ 2, Should Be Withdrawn

On pages 5-6 of the Office Action, claims 5 and 7-11 are rejected under 35 U.S.C. § 112, ¶ 2, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Claims 5 and 7-11 are first rejected because alphanumeric terms, such as SN-38 and GG-211, allegedly have not been adequately defined in the specification or claims. Applicants respectfully traverse this rejection.

The alphanumeric terms used in the claims are the names of topoisomerase inhibitors that are commonly used and recognized by those of ordinary skill in the art. For example, SN-38 is chemically named as 7-ethyl-10-hydroxycamptothecin (*Cancer Chemotherapy and Biotherapy: Principles and Practice*, 3rd Ed. (2001) at page 581); GG-211, also known as GI 147211, is 7-(4-methylpiperazinomethylene)-10,11-ethylenedioxy-20(S)-camptothecin (Emerson *et al.*, *Cancer Res.* 55(3): 603-609 (1995)); UCE6 is 1,3,8,10,11-pentahydroxy-2-methyl-10-(2-oxo-4-hydroxypentyl)naphtahcene-5,12-dione (Fujii *et al, J. Antobiot.* (Tokyo) 50(6): 490-495 (1997)); NB-506 is 6-N-formylamino-12,13-dihydro-1,11-dihydroxy-13-(β-D-glucopyranosil)-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione (Takenaga *et al.*, *Drug Metab. Dispos.* 27(2): 205-212 (1999)); IST-622 is 6-O-(3-ethoxypropionyl)-3',4'-O-exo-benzylidenechartreusin (Tashiro *et al.*, *Cancer Chemother. Pharmacol.* 34(4): 287-292 (1994)); and XR-5000, also known as DACA, is N-[2-(dimethylamino)ethyl]acridine-4-carboxamide (*Cancer Chemotherapy and Biotherapy: Principles and Practice*, 3rd Ed. (2001) at page 579). The other alphanumeric terms recited by the claims also have unambiguous meanings known by those of ordinary skill in the art. For this reason, Applicants respectfully

submit that claims 5 and 7-11 are not indefinite. MPEP § 2173.05(t) (citing *Martin v. Johnson*, 454 F.2d 746 (C.C.P.A. 1972) ("Chemical compounds may be claimed by a name that adequately describes the material to one skilled in the art.")).

Claims 8-11 are next rejected as allegedly indefinite because the amount of irinotecan or SN-38 recited in the claims are expressed in a concentration range. The concentration unit used in the claims (*i.e.*, mg/m^2) means the amount in mg used per m^2 of the patient's body area. This unit is widely used in the pharmaceutical industry, especially in connection with the treatment of cancer using parenterally delivered drugs, as it is important to determine the appropriate amount to be used according to the size of the patient in treating cancers. *See, e.g., Physician's Desk Reference*, 54th Ed., page 2412-2418 (2000), which was submitted as Document BK in the Information Disclosure Statement filed February 8, 2002. For this reason, Applicants respectfully submit that the pending claims are not indefinite, and the rejection under 35 U.S.C. § 112, ¶ 2, should be withdrawn.

The Rejection Under 35 U.S.C. § 103 Should Be Withdrawn

On pages 6-9 of the Office Action, claims 1-11 are rejected as allegedly obvious over Marx *et al.*, *Proc. Am. Soc. Clin. Oncology* 18: 454a (1999) ("Marx"), in view of Pitot *et al.*, *Journal of Clinical Oncology* 15(8): 2910-2919 (1997) ("Pitot") and U.S. Patent No. 5,622,959 to Priel *et al.* ("the '959 patent"). In particular, it is alleged that because Marx discloses an antiangiogenic effect of thalidomide and Pitot and the '959 patent disclose antitumor activities of CPT-11 and CPT, respectively, the claimed invention is obvious. Applicants respectfully traverse this rejection for the following reasons.

As the Examiner is aware, three basic criteria must be met in order to establish a case of *prima facie* obviousness: first, there must have been a motivation to combine the cited references at the time the invention was made; second, the alleged prior art must disclose or suggest all of the limitations of the claims alleged to be obvious; and third, there must have been at the time of the invention a reasonable expectation of success. MPEP §2142. Furthermore, hindsight cannot be used to reject a claim as obvious. MPEP § 2141.01. Consequently, when determining whether or not a claimed invention is obvious, one must cast her "mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." *In re*

Dembiczak, 175 F.3d 994, 999 (Fed.Cir. 1999) (reversing a determination that several claims were obvious over a combination of references that disclosed all of their limitations, but which did not provide a motivation to combine those limitations). Applicants respectfully submit that these criteria are not met by the combination of Marx, Pitot, and the '959 patent.

The Examiner, citing *Ex parte Quadranti*, 25 U.S.P.Q.2d 1071 (Bd. Pat. Appl. & Inter. 1992), alleges that the co-administration of two components, each of which is recognized as having anticancer activity, would have been obvious "in the absence of some proof of a secondary nature or some specific limitations which would tip the scale of patentability in favor of the claimed invention." Office Action at page 9. Applicants respectfully submit that such proof can be found in the application as filed.

As indicated in the specification, this invention is based, in part, on the ability of thalidomide to: (1) treat cancer; (2) improve the efficacy of other chemotherapeutic or radiation therapies for cancer; or (3) lessen the severity of certain dose-limiting toxicities of other anticancer drugs. The specification, page 11, line 38 - page 12, line 3. Thus, when thalidomide is co-administered with irinotecan to patients with metastatic colorectal cancer, a remarkable absence of gastrointestinal toxicity typically associated with irinotecan is observed. *Id.* at page 31, line 24 - page 32, line 21. None of the cited references disclose or even suggest this remarkable effect.

In addition, thalidomide was not an approved anticancer agent at the time of this invention, while numerous other agents known to be effective in treating cancer were. As such, these references would not have provided the necessary motivation to combine thalidomide with a topoisomerase inhibitor because one of ordinary skill in the art would have been likely to combine other known anticancer agents first with topoisomerase inhibitors. Thus, Applicants respectfully submit that the rejection under 35 U.S.C. § 103 could only be made with the aid of an impermissible hindsight. *Dembiczak*, 175 F.3d at 999. Similarly, the cited art certainly would not have provided any suggestion that the claimed invention would be successful. For these reasons, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

Conclusion

For the foregoing reasons, Applicants respectfully submit that claims 1-11 are allowable. No fee is believed due for this submission. However, should any fees be due for this submission or to avoid abandonment of the application, please charge such fees to Pennie & Edmonds LLP Deposit Account No. 16-1150.

Respectfully submitted,

Date August 17, 2003

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